composition of claim 53.

--67. (New) The method of claim 66, wherein the cancer is of epithelial origin.--

--68. (New) The method of claim 66, wherein the cancer is of neuroectodermal origin.--

--69. (New) The method of claim 68, wherein the cancer of neuroectodermal origin is a melanoma.--

--70. (New) The method of claim 66, wherein the administering is effected at two or more sites.--

--71. (New) The method of claim 70, wherein the administering is effected at three sites.--

REMARKS

Claims 1-4, 6-20, and 44-52 are pending in this application. By this Amendment, applicants have canceled claims 1-4, 6-20 and 44-52 without prejudice to applicants' right to pursue the subject matters in a future continuation application. Applicants have added new claims 53-71. Support for new claim 1 may be found inter alia on page 11, lines 13-20, page 54, lines 12-14, page 65, lines 12-15, page 85, lines 9-14. Support for new claims 2-11 may be found inter alia from pages 11 to 14. Support for new claim 12 may be found inter alia on page 43, lines 4-9. Support for claims 13-19 may be found inter alia on page 15, beginning line 27 to page 18, line 9. Accordingly there is no issue of new matter and applicants respectfully request the entry of this Amendment. Upon entry, claims 53-71 are under examination.

Specification

Applicants acknowledge the Examiner's rejection and will provide a new Figure 6, labeling the y-axis as IgG antibodies.

Double Patenting

Applicants acknowledge the Examiner's withdrawal of the provisional rejection.

Obviousness-type Double Patenting

The Examiner provisionally rejected claims 1-4, 6-20 and 44-52 under Judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-20 and 44-52 of copending application no. 08/475,784. The Examiner provisionally also rejected claims 1-4, 6-20 and 44-52 under judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44, and 46-56 of copending application nos. 08/477,147 and 08/481,809.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this application, applicants have hereinabove canceled claims 1-4, 6-20 and 44-52 without prejudice. Applicants have added new claims 53-71 in this subject application and will add new claims in the applications, U.S. Serial Nos. 08/475,784, 08/477,147 and 08/481,809. Applicants believe that the added new claims in the applications will obviate this ground of rejection.

35 U.S.C. §112 Rejections

The Examiner stated that the prior rejection of claims 4, and 13-17 under 35 U.S.C. §112, second paragraph, is withdrawn in view of applicants' arguments.

The Examiner rejected claims 1-4, 6-20 and 44-52 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed on July 10, 1996.

The Examiner stated that applicants essentially argue the reference by Fung, et al. should not be used to question whether antibodies against the ganglioside conjugate vaccines will prevent cancer since the experiments as set forth by Fung, et al. were not used to study whether GM2-KLH conjugated vaccine prolonged survivability. The Examiner stated that applicants further argue there is no evidence by Fung, et al. that the cancer cells express GM2, nor the antibodies to GM2 were generated after vaccination. The Examiner stated that applicants arguments are not persuasive to obviate the rejection. The Examiner stated that whether or not the objective of Fung, et al. experiments was to determine the efficacy of the GM2-KLH conjugated vaccine is not sufficient to overcome the rejection. The Examiner further stated that as set forth previously since the production of high titers of antibodies in melanoma patients with the GM2-KLH does not appear to correlate with the prevention of cancer as exemplified by the teachings of Fung, et al., it is unpredictable if the composition as claimed is efficacious as a vaccine. The Examiner stated that beyond this applicants arguments are not sufficient to obviate the rejection since the art as exemplified by Cohen, et al., (see Science 262:841-843, especially page 843) states: "Cancer vaccines are highly experimental." The Examiner further stated that since the specification provides insufficient guidance of how to use the composition as a vaccine and the art at the time of the invention set forth cancer vaccines are highly experimental, it is reasonable to conclude a skilled artisan would be forced into undue

experimentation to practice the claimed invention.

The Examiner further stated that applicants' amendment is sufficient to obviate the objection to the specification for the use of other gangliosides or chemically modified gangliosides. The Examiner further stated that the specification provides insufficient guidance of how to use derivatives of KLH as recited. The Examiner stated that applicants assert that by routine experimentation, one skilled in the art is enabled to make derivatives of KLH. The Examiner stated that applicants arguments are not persuasive.

The Examiner further stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess, et al.). The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar, et al.). The Examiner further stated that Rudinger, et al. teaches "particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori, but must be determined from case to case by painstakingly experimental study." The Examiner further stated that Salgaler, et al. teaches modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. The Examiner further stated that Fox, et al. teaches methods for determining fragments which have antigenic activity is unpredictable. These references demonstrate that an even a single amino acid substitution or what appears to be an inconsequential

chemical modification, will often dramatically affect the biological activity of a protein. The Examiner further stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

In response, applicants respectfully traverse the above ground of rejection. Applicants have hereinabove canceled claims 1-4, 6-20 and 44-52 without prejudice. New claims are directed to a composition comprising GM2 or GD2 ganglioside conjugated through the ceramide portion of the ganglioside to an immunogenic protein, a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier and uses of said composition. Accordingly, new claims are not directed to vaccine and thereby render the rejection to the vaccine claims moot.

Regarding the Examiner's comments about other ganglioside, applicants' independent claims are now directed to GM2 or GD2 ganglioside. These conjugated gangliosides have been fully enabled by the specification. Applicant believe that the amended claims have obviated this ground of rejection.

Regarding the Examiner's statements about the derivatives of Keyhole Limpet Hemocyanin, applicants maintain that the specification have provided enabling teachings to generate such derivatives. See Specification page 12, lines 4-13. Applicants have also described some routine experiments on page 4, second paragraph of the January 6, 1997 Supplemental Communication in Response to June 10, 1996 Office Action to generate said derivatives. Regarding the Examiner's specific comments about the

variation of one or a few amino acids which may change the property of a protein, the disclosed specification has provided specific embodiments of Keyhole Limpet Hemocyanin being used as the immunogenic protein. The derivatives generated may easily be tested using the specific Keyhole Limpet Hemocyanin disclosed in the specification for comparison. Accordingly, there is no undue experimentation and applicants maintain that the derivatives of Keyhole Limpet Hemocyanin are fully enabled by the specification as filed.

In view of the foregoing discussion, applicants respectfully request the reconsideration and withdraw of the above ground of rejection.

35 U.S.C. §103 Rejections

The Examiner rejected claims 1-3, 6-12, 18-20, 44, and 48-52 under 35 U.S.C. §103(a) as being unpatentable over Livingston, et al. (Cancer Research) in view of Ritter, et al., Livingston, et al. (U.S. Patent No. 5,102,663) and Ritter, et al. (1990) for the reasons set forth in the Office Action mailed on June 10, 1996.

The Examiner stated that in response to applicants' piecemeal analysis of the references (see Paper No. 11; pages 12-13; pages 7 and 8 of Paper No. 12), one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references. The Examiner stated that applicants assert that the cited references (see Paper No. 11; page 11) do not suggest or motivate one of ordinary skill in the art to make the claimed invention. The Examiner further stated that applicants arguments are not persuasive for the reasons as set forth in the last Office Action (see Paper No. 9; page 8).

The Examiner further stated that applicants appear to argue that the rejection should be withdrawn since from the prior art (e.g. Ritter, et al.) does not suggest or provide an expectation that the oligosaccharide portion of ganglioside conjugate remains intact or needs to be intact. The Examiner further stated that applicants arguments are not persuasive to obviate the rejection since applicants arguments are not commensurate in scope with the claimed invention. The Examiner further stated that the claimed invention does not set forth that the oligosaccharide portion remains intact. The Examiner stated that beyond this while Ratter, et al. (1991) may not characterize that the oligosaccharide portion remains intact with conjugation as asserted by applicants it would have been reasonable to expect the conjugate of the prior art would have the same properties of the conjugate as claimed since conjugating the KLH to a ganglioside as set forth by Ritter, et al. and as recited enhances the antibodies response.

The Examiner further stated that applicants argue that the rejection should be withdrawn since the prior art does not teach of the requirements (e.g. need) for an adjuvant. The Examiner further stated that applicants argument is not persuasive since Livingston, et al. sets forth the vaccine administered to melanoma patient contains an adjuvant. The Examiner further stated that for the reasons set forth above and in the last Office Action, said rejection is maintained.

In response, applicants respectfully traverse the above ground of rejection. Applicants would like to point out the applicants have canceled claims 1-4, 6-20 and 44-52 without prejudice. New claims are directed to a composition comprising GM2 or GD2 ganglioside CONJUGATED THROUGH THE CERAMIDE PORTION of the ganglioside to an immunogenic protein, a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable

carrier and uses of said composition.

Applicants maintain the cited references, alone or in combination thereof do not disclose, teaches or suggest the conjugation of GM2 or GD2 through the ceramide portion of the ganglioside to an immunogenic protein. The cited references, alone or in combination thereof, do not provide any SPECIFIC teaching that the conjugation should be carried at the ceramide portion. In addition, applicants further maintain that the cited references do not disclose, teaches or suggest the composition comprising the above GM2 and GD2 conjugates and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree.

Accordingly, in view of the foregoing, applicants respectfully request the reconsideration and withdraw of the above ground of rejection.

The Examiner rejected claims 4, and 13-17 under 35 U.S.C. 103(a) as being unpatentable over Livingston, et al. (Cancer Research) in view of Ritter, et al., Livingston, et al. (U.S. Patent No. 5,102,663) and Ritter, et al. (1990) as applied to claims 1-3, 6-12, 18-20, 44, and 48-52 above and further in view of Cancel, et al. and Mariani, et al. for the reasons set forth in the Office Action mailed on June 10, 1996.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of the subject application, applicants have canceled claims 4, 13-17 without prejudice, thereby rendering this ground of rejection moot. Independent claim 53 now recites the adjuvant which is a carbohydrate derviable from the bark of a Quillaja saponaria Molina tree, which is the subject matter of claim 4. Applicants believe that the Examiner's comments have been addressed by the response to

the above ground of rejection.

The Examiner rejected claims 45-47 under 35 U.S.C. 103(a) as being unpatentable over Livingston, et al. (Cancer Research) in view of Ritter, et al., Livingston, et al. (U.S. Patent No. 5,102,663) and Ritter, et al. (1990) as applied to claims 1-3, 6-12, 18-20, 44, and 48-52 above and further in view of Irie, et al. for the reasons set forth in the Office Action mailed on June 10, 1996.

The Examiner further stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to claims 1-3, 6-12, 18-20, 44, and 48-52 above. The Examiner further stated that for the reasons set forth above, applicants arguments are not persuasive. The Examiner further stated that applicants argument that the teaching that GM2 is found on melanomas and breast carcinomas by Irie, et al. does not provide sufficient motivation for one of ordinary skill in the art to practice the claimed invention is not persuasive. The Examiner further stated that since Livingston, et al. teaches of a vaccine for melanoma patients which stimulates the production of anti-GM2 antibodies and GM2 is associated with a variety of tumors (i.e. melanoma and breast) as taught by Irie, et al., one of ordinary skill in the art would have been motivated to use the vaccine composition not only melanomas as set forth by Livingston, but also breast carcinomas since both types of tumors have GM2 present. The Examiner further stated that for the reasons set forth above and in the last Office Action said rejection is maintained.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this subject application, applicants have hereinabove cancel claims 45-47 without prejudice. New claim 67 corresponds to the canceled claims

47 except that it ultimately depends on claim 53 recites a composition comprising a GM2 or GD2 ganglioside conjugated through the ceramide portion of the ganglioside to an immunogenic protein, a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier. The additional citation of Irie et al. in combination with the previous cited reference does not render the composition claim, claim 53 obvious and therefore cannot render the dependent claim 67 obvious. Accordingly, applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the July 11, 1997 Office Action and earnestly solicit allowance of the claims now pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the FOUR HUNDRED AND SEVENTY-FIVE DOLLAR ($475.00) fee for a three-month extension of time is deemed necessary in connection with the filing of this Amendment.

However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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Albert Wai Kit Chan 1/12/98
Albert Wai-Kit Chan Date
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